Testimony
of
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Gene-Environment Interactions as the New Research Model in Environmental Health

I appreciate this opportunity to talk with you about environmental influences on our health. This subject is timely because here at the beginning of a new century we are assembling the tools that will enable us to detect environmental triggers of disease more precisely and more meaningfully. This ability will come about because of advances in an entirely different field, that of genomics which is the study of genes and of what genes do. The Human Genome Project, which has been the topic of much recent press coverage, was initiated in part to determine what genes are important in disease development. What we are finding, though, is that few genes serve as major determinants of disease risk. Instead, it is the interaction of our genes and our environmental exposures that sets the stage for the majority of disease development. Indeed, for many diseases, our genetic makeup by itself accounts for only a small part of our disease risk. It is our environment, acting in concert with our particular genetic susceptibilities, that confers a major part of our disease risk. Thus gene-environment interaction is where our attention must focus and where the major strides in environmental health research will be made in the future. In my testimony I will (1) describe some of the work that illustrates the significant role of environmental factors in major diseases, (2) describe how understanding gene-environment interactions will improve our ability to identify the precise environmental triggers of diseases, and (3) give examples of some of the research that NIEHS has initiated to address these topics. I will also touch on our expanded view of what constitutes "environment" and how diet and socioeconomic status must be included in this view.

The past few years have seen a remarkable number of studies that have identified the importance of environment in major diseases. By comparing rates among fraternal and identical twins, scientists have been able to tease apart the relative contributions of genes and of environment for several major diseases. Based on twin studies in Scandinavia, we now know that environment accounts for more than 50% of cancer risk, with genes accounting for the remainder of risk. Twin studies on Parkinson's Disease reveal that environment accounts for 85% of the risk in the late-onset cases of this disease. For autoimmune diseases such as multiple sclerosis and Lou Gehrig's Disease, environmental factors account for 60% to 75% of disease risk. Clearly, then, our environment is a major determinant of our health and of our relative risk for disease. It also spans a broad number of diseases and disorders. To give you an example, at the National Institute of Environmental Health Sciences we are investigating environmental triggers for cancer, Parkinson's Disease, birth defects, infertility, autoimmune diseases, hypertension, asthma and other respiratory disorders, learning and behavioral disorders, and uterine fibroids.

Although many people think of "environment" in terms of pollutants and industrial by-products, environmental factors encompass a much larger universe. They include diet and nutrients, pharmaceuticals, infectious organisms, natural compounds such as aflatoxin found in grains, herbal formulations, and our socio-economic environment. It is this totality of environmental factors that is proving to have a major role in human health and in disease development.

Environment, though, is not the total answer in disease development. Two people with the same exposure can have very different outcomes. Obviously not everyone who smokes cigarettes gets lung cancer, nor does every asthmatic respond to dust mite and cockroach allergens. We all have different susceptibilities to environmental agents. Many of these differences in susceptibility appear to be due to variations in genes coding for proteins critical in

the body's response to environmental agents. These proteins include metabolizing enzymes, DNA repair enzymes, cell cycle control proteins, cell signaling proteins, and receptor proteins. Someone inheriting a gene that produces a weak or ineffective form of one of these critical proteins will be more susceptible than someone inheriting a gene that produces a more effective form. That is because the first person might be less able to break down or excrete environmental compounds or to repair cellular damage caused by environmental agents. Thus understanding gene-environment interactions is critical in defining the environmental contribution to disease. Neither acts alone. It is the two acting in concert that lays the foundation for disease and dysfunction.

For these reasons the National Institute of Environmental Health Sciences (NIEHS) established the Environmental Genome Project (EGP). The EGP is a survey of the important genetic variants that affect people's responses to environmental agents. The EGP is a natural outgrowth of the Human Genome Project. In fact, understanding gene-environment interactions will be the only way to extract the full benefit from our investments in the Human Genome Project. That is because only a few, relatively rare, diseases are caused by defects in a single gene. A large number of diseases and disorders result from inadequacies in common environmental response genes and can only lead to disease in the presence of a particular exposure.

The Environmental Genome Project ushers in a new era for environmental health science research. Previously individual variation in responsiveness to exposures generated a high "background noise" that could often mask the contribution of environmental agents to disease risk, particularly at the low levels to which most of us are exposed. Now, as we identify important genetic variants that alter response to environmental agents, scientists can better control for the confounding variable of individual susceptibility when they study environmentally caused diseases. In the future, we expect to be able to follow up on results of

twin studies by identifying the actual environmental components that comprise the major part of disease risk.

It should be noted, though, that timing is everything for environmental exposures. Certain stages of life impart a much greater vulnerability. Early human development, infancy, and childhood are among these stages. The carefully orchestrated events by which a fertilized cell develops into a sentient being offer many opportunities for environmental interference and disruption. In fact, children can suffer adverse effects from environmental exposures at doses that cause no apparent problems in adults.

We are greatly interested in the potential of birth registries and prospective cohorts to decipher the genetic and environmental contributions to many diseases, particularly in children. We have joined with the Norwegian government on a study of cleft palate, a common birth defect. Norway has one of the highest reported rates of cleft palate in the world, as well as a highly organized birth registry that records these defects. For this study, both genetic samples and data on environmental exposures of mothers and infants are being collected. When completed, this study will provide the largest and most comprehensive collection of data ever obtained on the genetic and environmental components of this birth defect.

The NIEHS is also building on plans currently under way in Norway to recruit 100,000 pregnant women and their children. These families would be followed in a lifetime cohort study of health. NIEHS will collect and store blood and urine of these women for the purpose of assessing environmental and other exposures during pregnancy. This information on exposures of the fetus will be used to study the effects of environmental factors during this crucial period on birth defects, developmental problems, childhood diseases, and even diseases of adulthood that result from exposures early in life. In addition, NIEHS, CDC, and the National Institute of Child Health and Human Development have the lead for a similar longitudinal study on environmental influences on children's health in this country. This study was recommended by

the President's Task Force on Environmental Health Risks and Safety Risks to Children in 1998 and mandated by the Children's Health Act of 2000.

Another study under design at NIEHS is the Sisters Study of breast cancer. This study would examine environmentally associated risks of breast cancer by recruiting women who have a sister already diagnosed with breast cancer. Because these women are at increased risk of breast cancer, twice as many breast cancer cases are expected as would be identified in any other cohort of similar size. Biologic specimens will be collected and stored at recruitment, and extensive questionnaires will be submitted regularly. Breast cancer risk will be assessed in terms of exposure to natural hormones, environmental hormone disruptors, growth factors, dietary components, and environmental contaminants such as pesticides and solvents. This study will also assess the importance of gene-environment interactions.

Studies continue to validate the importance of nutrition in maintaining health and preventing disease. Whole grain foods, for example, have been identified in NIEHS rodent studies as being protective against breast cancer and have been shown to protect against stroke in a NIH-supported longitudinal study of nurses. Nutrition is a major environmental risk component of many diseases. For this reason, the NIEHS has partnered with the NIH Office of Dietary Supplements (ODS) to fund a Center for Phytochemical and Phytonutrient Studies. This center is currently investigating the ability of dietary phytochemicals to prevent or treat prostate cancer, the role of phytoestrogens in altering immune response and possibly predisposing some women to autoimmune diseases, and the capacity of bioflavonoids to protect brain tissue from oxidative damage.

One of the major environmental challenges we face is that of exposure assessment – that is, defining exactly what chemicals are in our environment and how much is absorbed in our bodies. This type of information is invaluable to the NIEHS in designing relevant epidemiologic and laboratory studies that can determine the types of effects that can arise from environmental exposures. The NIEHS collaborates with the United States Geological Survey and the Centers for Disease Control and Prevention to use their expertise and databases to develop a better understanding of common environmental exposures in this country. We are also collaborating with our sister agency, the National Cancer Institute, on the Agricultural Health Study. In this study we are assessing exposures common to agricultural settings and evaluating their influence on risk of developing conditions such as cancer, Parkinson's, infertility, birth defects, respiratory dysfunction, and other problems.

In conclusion, I would like to make the case that preventing disease is one of the most important services of our public health network. Protecting people from avoidable illness and death saves money, spares suffering, and improves the quality of life for society. The most effective way to prevent disease and disability is to understand the cause of an illness and change the conditions that permit it to occur. A key strategy to prevent many diseases or delay disease progression is to minimize or eliminate adverse effects of chemicals in the environment. This preventive strategy underlies the field of environmental health and is a core principle guiding NIEHS-funded research.

Because of its emphasis on prevention, environmental health science research is rarely played out in the high-tech, treatment-oriented arena of modern clinical centers. Rather, some of our most important work is done in agricultural fields, among migrant workers, in inner-city neighborhoods, and in public schools. The practice of environmental health science often requires engaging the efforts of our most disadvantaged citizens. NIEHS has been

experimenting with new models of research that provide for citizen participation. It is our feeling that citizen-based participatory research will generate more relevant findings, will suggest better real-world research questions, and will serve as a communication tool for the participants and their neighbors.

I would be pleased to answer any questions.